Summary Table of Study Protocol

Title	A Cross-sectional Survey to Evaluate Physician Knowledge of Safety Messages Included in the Physician Education Booklet (PEB) for IMLYGIC®
Protocol version identifier	Superseding Amendment **3, version 1.0**
Date of last version of the protocol	**17 July 2019**
EU Post Authorization Study (PAS) Register No	**EUPAS31188**
Active Substance	Talimogene Laherparepvec (T-VEC)
Medicinal Product	IMLYGIC
Product Reference	EMEA/H/C/002771
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	The overall objective of this study is to evaluate awareness of the IMLYGIC PEB and knowledge of the key messages included in the IMLYGIC PEB among physicians who completed the required IMLYGIC training. Primary - To evaluate physicians' knowledge levels of the key messages included in the IMLYGIC PEB Secondary - To evaluate physicians' levels of receipt and reading of the IMLYGIC PEB - To evaluate the physician's understanding of the requirements to distribute the Patient Safety Brochure and Patient Alert Card
Country(ies) of Study	Austria, Germany, the Netherlands, United Kingdom (UK)

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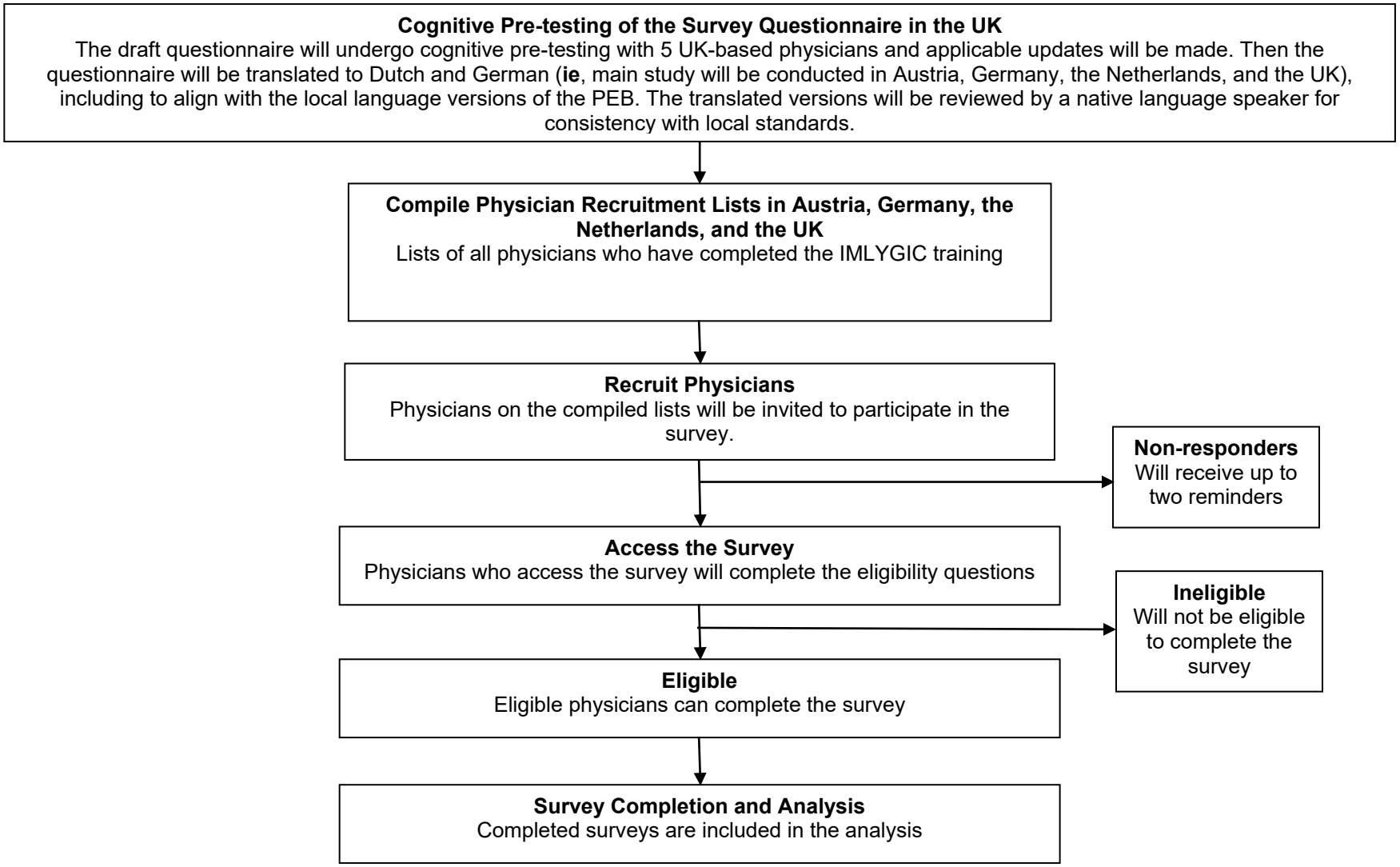
Study Design Schema



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2. List of Abbreviations

Abbreviation	Description
AE	adverse event
ADR	adverse drug reaction
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DRR	durable response rate
EDC	electronic data capture
EMA	European Medicines Agency
FMV	fair market value
GM-CSF	granulocyte macrophage colony-stimulating factor
GVP	Good Pharmacovigilance Practice
HCP	healthcare professional
HSV-1	herpes virus type 1
IEC	independent ethics committee
PASS	post-authorisation safety study
PEB	Physician Education Booklet
RMM(s)	risk minimisation measure(s)
RMP	risk management plan
SAP	statistical analysis plan
SmPC	summary of product characteristics
SOP	standard operating procedure
SQETCF	Site Qualification and Education & Training Confirmation Form
UK	United Kingdom

3. Responsible Parties

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4. Abstract

- **Study Title**

  A Cross-sectional Survey to Evaluate Physician Knowledge of Safety Messages Included in the Physician Education Booklet (PEB) for IMLYGIC®

- **Study Background and Rationale**

  An estimated 100,000 new cases of melanoma were diagnosed and over 22,000 deaths occurred in Europe in 2012. The age-standardised incidence rate of melanoma is estimated to be approximately 11 per 100,000 in Europe, however, incidence rates vary widely across Europe. In Europe, the 5-year survival rate is on average 83%, however, survival decreases with more advanced stage of disease and varies widely.

  Since 2011 the treatment landscape for patients with advanced melanoma has changed rapidly to include immunotherapy such as checkpoint inhibitors, targeted agents (eg, BRAF and MEK inhibitors), and oncolytic immunotherapy. Oncolytic viruses are a new treatment modality in melanoma. Talimogene laherparepvec (IMLYGIC®) is a herpes simplex virus type-1-derived oncolytic immunotherapy designed to selectively replicate within tumours and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumour immune responses. In the open-label phase III trial (OPTiM), IMLYGIC showed an increase in durable response rate (DRR) compared to GM-CSF treatment, with a DRR of 25.2% compared to 1.2%, respectively, in patients with unresectable regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) melanoma who had no bone, brain, lung, or other visceral disease. Based on the positive OPTiM trial results, the European Medicines Agency (EMA) approved IMLYGIC on 17 December 2015. IMLYGIC is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung, or other visceral disease. IMLYGIC is the first oncolytic viral drug to treat unresectable and metastatic melanoma. IMLYGIC is directly injected into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance.

  Due to its viral nature, IMLYGIC presents potential risks of primary herpetic infection during treatment and/or reactivation from latent state after treatment. In addition, IMLYGIC presents potential risks of stimulation or reactivation of latent wild-type Herpes Simplex Virus Type 1 (HSV-1) in patients. Furthermore, secondary transmission and infection by IMLYGIC can occur among patients' close contacts

and healthcare providers (HCPs). Herpetic infection can present clinically as oral or genital herpes, herpetic whitlow, or herpetic gladiatorum of the skin, herpetic keratitis, herpetic conjunctivitis, herpetic uveitis, herpetic encephalitis, and disseminated herpetic infection. To ensure safe administration and handling, IMLYGIC was authorised with additional risk minimisation measures (RMMs) in Europe. These additional RMMs include a controlled distribution programme, educational material targeted for both HCPs and patients, with the primary aim to inform HCPs and patients and their close contacts about the potential risks associated with IMLYGIC.

For HCPs, the primary additional RMM is the Physician Education Booklet (PEB), which includes information on the safe administration and handling of IMLYGIC. In accordance with European pharmacovigilance legislation introduced in 2012 and Good Pharmacovigilance Practice (GVP), the effectiveness of additional RMM should be evaluated. This survey is classified as a post-authorisation safety study (PASS, category 3) and this study will be designed and conducted in accordance with GVP Modules VIII and XVI.

- **Research Question and Objective(s)**

  Primary Objective(s)

  The primary objective is to evaluate physicians' knowledge levels of the key messages included in the IMLYGIC PEB among physicians who completed the required IMLYGIC training, specifically:

  - risk of disseminated herpetic infection in immunocompromised individuals,
  - risk of accidental exposure or transmission of IMLYGIC to close contacts or HCPs,
  - risk of symptomatic herpetic infection due to latency and reactivation of IMLYGIC or wildtype herpes in patients,
  - IMLYGIC use in pregnancy,
  - safe use and handling of IMYLIGIC, and
  - important accompanying patient materials.

  Secondary Objective(s)

  - To evaluate physicians' levels of receipt and reading of the IMLYGIC PEB among physicians who completed the required IMLYGIC training, and
  - To evaluate physicians' understanding of the requirements to distribute the Patient Information Leaflet (PIL), Patient Safety Brochure, and Patient Alert Card.

  An exploratory objective is a composite variable on physicians' knowledge levels for all 6 primary endpoints; specifically, the distribution of percentages of physicians who provide correct responses to all 6 of the knowledge-related questions.

- **Study Design/Type**

  This is a multi-national, non-interventional, cross-sectional survey study.

- **Study Population**

  The target population is physicians who completed the required IMLYGIC training in Austria, Germany, the Netherlands, and the United Kingdom. Based on the current number of physicians who have completed the required IMLYGIC training, it is anticipated that up to 125 HCPs will be invited to participate in the study using lists of physicians obtained from the IMLYGIC controlled distribution programme.

- **Summary of Physician Eligibility Criteria**

  Inclusion criteria

  - Has completed the controlled distribution programme training
  - Has provided permission to share their responses in aggregate with the EMA or national competent regulatory authorities, if requested

  Exclusion criteria

  - Has participated in the cognitive pre-testing of the survey questionnaire to be used for this study
  - Has been a direct employee of Amgen, ICON, or the EMA within the year prior to completing the survey

- **Variables**
  - *Outcome Variable(s)*
    - Primary: Levels of knowledge of the key messages included in the IMLYGIC PEB, assessed as the percentages of physicians with correct responses to the knowledge-related questions. Success criteria for the primary endpoint percentages are the achievement of at least 80% of physicians being able to correctly respond to each knowledge-related question that has a minimum n = 30.
    - Secondary: Levels of awareness (receipt) and use (reading) of the IMLYGIC PEB, and levels of distributing the patient-directed materials to patients. Assessed as the percentages of physicians who report awareness/use/distribution.
    - Exploratory: a composite variable on the level of physicians'' knowledge for all primary endpoints
  - *Covariate(s)*
    - Physician characteristics

- **Study Sample Size**

  A sample of 30 to 50 completed physician surveys is targeted for this study. This sample size is determined based on both practical and statistical considerations.

  The primary evaluation criteria are the levels of physicians' knowledge of the key messages included in the IMLYGIC PEB. A sample size of 50 HCP respondents allows estimation of a minimum HCP knowledge level of at least 80% with a precision of 11.9%.

- **Data Analysis**

  The primary analysis population will include all physicians who have completed at least 1 of the endpoint questions in the survey. Frequencies, percentages, and corresponding 95% confidence intervals (CIs) will be used to summarise the endpoints for the primary analysis set overall, by country, and by subgroups (practice setting, primary medical **specialty**, and last time prescribed IMLYGIC). For each knowledge level question, the percentage of HCPs who answer each question correctly will be estimated and assessed against the 80% (± 95% CI) target. For secondary endpoints of receipt and reading of the PEB, and distribution of patient-directed materials, percentages and 95% CI will be estimated.

  The primary analysis will be performed by having read vs. not read the IMLYGIC PEB and also by prescribing status. An analysis to evaluate the impact of recall bias will be performed by repeating the primary analysis stratified by tertiles of time since physicians completed the required IMLYGIC controlled distribution training.

5. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	11 April 2019	**See Summary of Changes**		
2	17 July 2019	**See Summary of Changes**		
3	**14 October 2019**	**See Summary of Changes**		

6. Milestones

Milestone	Planned date
Cognitive pre-test	03-July 2019
Start of data collection	23 October 2019
End of data collection	28 February 2020
Final report of study results	22 June 2020

* These timelines are subject to receiving timely approvals from national competent authorities and ethics committees which may vary by country.

7. Rationale and Background

An estimated 100,000 new cases of melanoma were diagnosed and over 22,000 deaths occurred in Europe in 2012 (Ferlay *et al*, 2013). At a time when the incidence of some of the more common cancers has declined (such as lung cancer), the incidence of melanoma has increased consistently in Europe (eg, in the United Kingdom [UK], the age-standardised incidence rate of malignant melanoma increased by 278% between 1993 and 2014, though the projected rate of increase in incidence is likely to slow in future years) (Smittenaar *et al*, 2016). The age-standardised incidence rate of melanoma is estimated to be approximately 11 per 100,000 in Europe. However, incidence rates have varied widely across Europe, ranging between 1.3 per

100,000 population in Albania to 25.8 per 100,000 population in Switzerland. (Ferlay *et al*, 2013)

Detected early stage melanoma is associated with high patient survival rates, however, if attempted excision of the lesion is unsuccessful, there is a high likelihood of recurrence, with 75% recurring within 2 years and 95% within 5 years after initial diagnosis (Brantsch *et al*, 2008).

Although metastatic risk is low in most patients, approximately 85% of metastases involve regional lymph nodes, followed by distant metastasis in the skin, lung, liver, bone, and brain. The risk of locoregional recurrence or distant metastasis is dependent on the pathological tumour characteristics, such as tumour location (ear, lips, areas of chronic ulcers or inflammation), clinical size of lesion (> 2 cm in diameter), histological depth extension (beyond the subcutaneous tissue), histological type, and degree of differentiation, recurrence, and immunosuppression (Stratigos *et al*, 2015).

In Europe, the 5-year survival rate is on average 83% (Crocetti *et al*, 2015). However, survival decreases with worsening stage and varies widely. Five-year survival is estimated to be > 95% for Stage 1, 65-93% for Stage II, 41-71% for Stage III, and 9-28% for Stage IV (Svedman *et al*, 2016). The 5-year recurrence-free survival is estimated to be between 28% to 44% for Stage III.

7.1 Disease and Therapeutic Area

Since 2011 the treatment landscape for patients with unresectable or metastatic melanoma has changed rapidly to include immunotherapy (checkpoint inhibitors eg, anti-CTLA-4 [ipilimumab], anti-PD-1 [nivolumab, pembrolizumab]), targeted agents (BRAF and MEK inhibitors), and oncolytic viral therapy.

Systemic immunotherapies work to stimulate an individual's immune system to destroy cancer cells more effectively. Ipilimumab (Yervoy®), nivolumab (Opdivo®), and pembrolizumab (Keytruda®) are approved systemic therapies for unresectable and metastatic melanoma.

About 40-50% of melanomas have *BRAF* gene mutations and the majority of these mutations are $BRAF^{V600E}$ (80-90%) or $BRAF^{V600K}$ (10-20%). Melanoma patients with these *BRAF* mutations can be treated with *BRAF and MEK* targeted therapies. Approved targeted therapies include vemurafenib (Zelboraf®), dabrafenib (Tafinlar®), trametinib (Mekinist®), or a combination of dabrafenib plus trametinib.

Oncolytic viruses are another new treatment modality in melanoma. Talimogene laherparepvec (IMLYGIC®) is a herpes simplex virus type-1 genetically engineered to selectively replicate in, and kill, cancer cells without injuring normal tissues. IMLYGIC was approved as the first oncolytic immunotherapy to treat unresectable and metastatic melanoma.

7.1.1 Talimogene Laherparepvec (IMLYGIC)

Talimogene laherparepvec or IMLYGIC is a herpes simplex virus type-1-derived oncolytic immunotherapy designed to selectively replicate within tumours and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumour immune responses. IMLYGIC is directly injected into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance (Harrington *et al*, 2017; Summary of Product Characteristics, 2018).

In the open-label phase III trial (OPTiM), the efficacy of IMLYGIC was compared with subcutaneously administered GM-CSF in patients with unresectable Stage IIIB/C and IV melanoma (Andtbacka *et al*, 2015). Countries participating in the OPTiM trial included Canada, South Africa, United States, and the UK. IMLYGIC showed an increase in durable response rate (DRR) compared to GM-CSF treatment, with a DRR of 25.2% compared to 1.2%, respectively, in patients with unresectable regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) melanoma who had no bone, brain, lung, or other visceral disease (Andtbacka *et al*, 2015; Harrington *et al*, 2016).

Based on the positive OPTiM trial results, the European Medicines Agency (EMA) approved IMLYGIC on 17 December 2015 (EMA, 2015). IMLYGIC is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung, or other visceral disease.

Due to its viral nature, IMLYGIC presents potential risks of primary herpetic infection during treatment and reactivation from latent state after treatment. In addition, IMLYGIC presents potential risks of stimulation or reactivation of latent wild-type HSV-1 in patients and secondary transmission and infection by IMLYGIC among patients' close contacts and health care providers (HCPs). Herpetic infection can present clinically as oral or genital herpes, herpetic whitlow, or herpetic gladiatorum of the skin, herpetic keratitis, herpetic conjunctivitis, herpetic uveitis, herpetic encephalitis, and disseminated herpetic infection.

7.1.1.1 Additional Risk Minimisation Measures (RMMs)

To inform safe and effective use, IMLYGIC was authorised with additional risk minimisation measures (RMMs) in Europe. These additional RMMs include a controlled distribution programme, educational material targeted for both HCPs and patients, with the primary aim to inform HCPs and patients about potential risks associated with IMLYGIC.

7.1.1.1.1 Controlled Distribution Programme

The controlled distribution programme for IMLYGIC manages the product supply chain to ensure that cold storage requirements are observed and to control the distribution of IMLYGIC to qualified centres and to patients.

The controlled distribution programme is in place to ensure that the following requirements are fulfilled before IMLYGIC is dispensed:

- Experienced HCPs are adequately trained in order to minimise the risk of occurrence of specified adverse drug reactions (ADRs) in patients, HCPs, and close contacts of the patients,
- HCPs and support personnel (eg, pharmacists) are trained regarding safe and appropriate storage, handling, and administration of IMLYGIC, and clinical follow-up for patients treated with IMLYGIC,
- HCPs and support personnel are provided with safety information (Patient Safety Brochure and Patient Alert Card) to communicate with patients and their family and caregivers, and
- Trained HCPs will record batch number information in patients' charts and on the patients' alert cards for all injections and to provide the batch number when reporting ADRs.

In Europe, IMLYGIC has a controlled distribution programme and physicians need to complete required training delivered by Amgen medical liaisons before they are authorised to receive shipments of IMLYGIC. Hospital sites with resources and facilities who can satisfactorily handle and administer IMLYGIC are eligible for training and qualification. Mandatory participants of the training include 1 experienced physician in the treatment of melanoma and 1 pharmacist primarily responsible for handling IMLYGIC. Optional participants in the training can include nurses, other physicians potentially treating patients with IMLYGIC, another pharmacist, or other pharmacy staff handling IMLYGIC at the site. Upon completion of training, sites are provided with IMLYGIC risk minimisation materials (eg, Patient Safety Brochures and Patient Alert Cards). Training is also documented via a Site Qualification and Education & Training

Confirmation Form (SQETCF). Sites with evidence of SQETCF on file are authorised to be supplied with IMLYGIC.

7.1.1.1.2 Physician Education Booklet (PEB)

For HCPs, the primary additional RMM is the Physician Education Booklet (PEB), which includes information on the following:

- risk of disseminated herpetic infection in immunocompromised individuals,
- risk of accidental exposure or spread of IMLYGIC to close contacts or HCPs,
- risk of symptomatic herpetic infection due to latency and reactivation of IMLYGIC or wildtype herpes in patients,
- IMLYGIC use in pregnancy,
- safe use and handling of IMLYGIC, and
- important accompanying patient materials.

7.2 Rationale

In accordance with European pharmacovigilance legislation introduced in 2012 and Good Pharmacovigilance Practice (GVP) (European Commission, 2010), the effectiveness of additional RMM described in the Risk Management Plan (RMP) should be evaluated. The objective of this survey study is to measure the effectiveness of the additional RMM for IMLYGIC. Specifically, to measure knowledge and understanding of the information in the HCP-directed additional RMM for IMLYGIC. This survey is classified as a post-authorisation safety study (PASS, category 3) and this study will be designed and conducted in accordance with GVP Modules VIII and XVI (European Medicines Agency, 2017a; European Medicines Agency, 2017b).

The proposed study utilises a cross-sectional survey study design. In Europe, Module XVI of GVP, selection of tools and effectiveness indicators of RMMs, references the use of “scientifically rigorous survey methods” to assess the awareness of the target audience and the level of knowledge achieved by educational interventions and/or information provision (European Medicines Agency, 2017b).

7.3 Statistical Inference (Estimation or Hypothesis[es])

This study is a survey to estimate physicians’ knowledge levels of the information included in the IMLYGIC RMMs. The results will therefore be descriptive in nature and no formal hypothesis will be tested.

8. Research Question and Objectives

The overall objective of this study is to evaluate physicians' awareness of the IMLYGIC PEB and knowledge of the key messages included in the IMLYGIC PEB.

8.1 Primary

The primary objective of this study is to evaluate physicians' knowledge levels of the key messages included in the IMLYGIC PEB among physicians who completed the required IMLYGIC training, specifically:

- risk of disseminated herpetic infection in immunocompromised individuals,
- risk of accidental exposure or transmission of IMLYGIC to close contacts or HCPs,
- risk of symptomatic herpetic infection due to latency and reactivation of IMLYGIC or wildtype herpes in patients,
- IMLYGIC use in pregnancy,
- safe use and handling of IMYLIGIC, and
- important accompanying patient materials.

8.2 Secondary

The secondary objectives of this study are:

- To evaluate physicians' levels of receipt and reading of the IMLYGIC PEB among physicians who completed the required IMLYGIC training, and
- To evaluate physicians' understanding of the requirements to distribute the PIL, Patient Safety Brochure and Patient Alert Card.

8.3 Exploratory

An exploratory objective is a composite variable on physicians' knowledge levels for all 6 primary endpoints.

9. Research Methods

9.1 Study Design

This is a multi-national, non-interventional, cross-sectional survey study to evaluate the effectiveness of the HCP-directed additional RMMs for IMLYGIC; specifically, the PEB. The survey will be conducted in a single wave in Austria, Germany, the Netherlands, and the UK among physicians that prescribe IMLYGIC. The target number of completed physician surveys is 30 to 50. The target groups are who completed the required IMLYGIC training.

The sampling frame of physicians eligible for study participation will be recruited from the population of physicians who have completed the required training for HCPs as part of

the IMLYGIC controlled distribution programme. Using the available physician contact details, invitations to participate in the survey will be sent to physicians by email (preferred) or by post mail (if email is not available). Data will be collected primarily by on-line electronic data capture (EDC). For contingency planning, a paper-based survey may be offered as an alternative mode of survey completion depending on survey response rates. Information collected will include the receipt and reading of the IMLYGIC PEB, knowledge of the key messages included in the IMLYGIC PEB, physicians' understanding of the requirement to distribution the Patient Safety Brochure and Patient Alert Card, and brief physician characteristics.

Prior to conducting the actual survey, the draft survey questionnaire will undergo cognitive pre-testing. The goals of cognitive pre-testing are to identify any survey questions that require clarification or revision based on areas of confusion revealed by physicians in the cognitive pre-test interviews, and to ensure that translated versions of the questionnaire are conceptually and cross-culturally equivalent in each of the local country languages to avoid misunderstanding.

The survey will be conducted by ICON, a vendor experienced in the design, conduct, and reporting of risk minimisation effectiveness surveys in Europe.

9.2 Setting and Study Population

The target population is physicians who completed the required IMLYGIC training in the 4 participating European countries. These countries were selected as a representative sample of the European countries where IMLYGIC is reimbursed for use. Specifically, countries with the largest use of IMLYGIC were selected to ensure a reasonable number of physicians will be available to recruit. In addition to considering market share, countries were selected to ensure reasonable geographic representation as well as study feasibility.

Based on the current number of physicians who have completed the required IMLYGIC training, it is anticipated that up to 125 physicians across all participating countries will be invited to participate in the study using lists obtained from the IMLYGIC controlled distribution programme.

The target groups for HCP training were established by Amgen as described in section 7.1.1.1.

9.2.1 Study Period

The minimum planned period for data collection is 3 months. As this is a single wave cross-sectional design, data from physicians will be collected at one point in time.

9.2.2 Healthcare Professional Eligibility

To determine physicians' eligibility, screening questions will be included prior to potential participants beginning the survey.

9.2.2.1 Inclusion Criteria

Physicians eligible for study inclusion are those who:

- completed the controlled distribution programme training, and
- provided permission to share their responses in aggregate with the EMA or national competent authorities, if requested.

9.2.2.2 Exclusion Criteria

Physicians will be excluded if they have:

- participated in the cognitive pre-testing of the survey questionnaire to be used for this study, or
- have been direct employees of Amgen, ICON, or the EMA within the year prior to completing the survey.

9.2.3 Matching

Not applicable.

9.2.4 Baseline Period

Not applicable. This is a cross-sectional study.

9.2.5 Study Follow-up

Not applicable. This is a cross-sectional study.

9.3 Variables

The survey questionnaire includes the following:

- survey introduction that describes the survey objective and logistics,
- screening questions to determine eligibility for survey participation,
- questions regarding the receipt and reading of the IMLYGIC PEB,
- questions to assess knowledge of the key messages included in the IMLYGIC PEB, specifically:
  - risk of disseminated herpetic infection in immunocompromised individuals,
  - risk of accidental exposure or transmission of IMLYGIC to close contacts or HCPs,

- risk of symptomatic herpetic infection due to latency and reactivation of IMLYGIC or wildtype herpes in patients,
- IMLYGIC use in pregnancy,
- safe use and handling of IMYLIGIC, and
- important accompanying patient materials,

- questions to assess understanding of requirements to distribute the Patient Safety Brochure and Patient Alert Card, and
- brief questions on physicians' characteristics.

Survey question types are multiple choice, yes/no, and true/false questions with no free text allowed.

9.3.1 Exposure Assessment

No tests or reference treatments are utilised in this cross-sectional, non-interventional survey of physicians.

9.3.2 Outcome Assessment

Measure of success

The results of the study will be interpreted considering an acceptable level of knowledge and awareness. The outcome estimates and associated 95% confidence intervals (CIs) will be calculated. The selection of a threshold for success is subjective and not based on *a priori* knowledge, experience, or established scientific criteria in the education or risk communication or evaluation literature. Therefore, the results will be contextualised with other available information.

Primary endpoints

The primary endpoints are the percentages of physicians with correct responses to the knowledge-related questions (risk of disseminated herpetic infection in immunocompromised individuals, risk of accidental exposure or transmission of IMLYGIC to close contacts or HCPs, risk of symptomatic herpetic infection due to latency and reactivation of IMLYGIC or wildtype herpes in patients, IMLYGIC use in pregnancy, safe use and handling of IMYLIGIC, and important accompanying patient materials). Success criteria for the primary endpoint percentages are at least 80% of HCPs provide a correct response to each individual knowledge-related question that has a minimum n = 30.

Secondary endpoints

The secondary endpoints are the percentages of physicians that recall receiving and reading the IMLYGIC PEB and distributing the patient-directed materials to their patients.

Exploratory endpoints

An exploratory endpoint is a composite variable on the level of physicians' knowledge across all knowledge-related questions; specifically, an overall score for each physician will be calculated that totals the correct responses to all 6 of the knowledge-related questions. The distribution (ie, percentage) of the number of physicians who correctly respond to the questions will be summarised (eg, 0, 1-5, 6-10, 11-15 questions correct).

9.3.3 Covariate Assessment

The following sociodemographic characteristics will be collected and used to describe the sample:

- Country
- Practice setting (academic/university-affiliated hospital/outpatient clinic, district/general hospital, outpatient clinic (not academic or university affiliated, other))
- Primary medical specialty – (dermatology, dermato-oncology, internal medicine, medical oncology, radiation oncology, general surgery, surgical oncology, other)
- Years practising as an HCP (< 5 years, 5-< 10 years, 10-< 15 years, ≥ 15 years, prefer not to answer)
- Last time prescribed IMLYGIC (< 1 month ago, 1 to 2 months ago, > 2 to 3 months ago, > 3 to 6 months ago, > 6 months ago, don't know/not sure)

9.3.4 Validity and Reliability

The survey questionnaire will undergo cognitive pre-testing with 5 HCPs prior to conducting the actual survey. This sample size is based on both qualitative research standards and feasibility considerations. In qualitative research, a sample of 12 interviews for homogeneous groups is considered to be sufficient to achieve saturation (saturation is the point in the data collection process where no new relevant information is elicited from individual interviews) (Guest *et al*., 2006). From a feasibility perspective, based on the limited use of IMLYGIC, it would be impractical to conduct pre-testing with 12 HCPs in each country. Based on experience conducting pre-testing with European-based HCPs for similar surveys, limited cultural adaptation may be required for this survey given the concepts being tested, where fewer (ie, 5-10) total interviews have routinely enabled saturation when performing pre-testing.

The goal of cognitive pre-testing is to identify any survey questions that require clarification or revision based on areas of confusion or miscomprehension revealed by HCPs in the cognitive pre-test interviews.

HCP pre-testing will be completed through 1-on-1 interviews. To be eligible to participate in the cognitive pre-test, physicians must have prescribed IMLYGIC within the last 12 months. Physicians will be recruited from an Amgen-provided list of HCPs. Due to an anticipated time commitment of 45 to 60 minutes to participate in the cognitive pre-test, physicians who complete the cognitive pre-test will receive fair market value (FMV) compensation if allowed per the local law and regulations.

During the conduct of the cognitive pre-test, the survey questionnaire will be presented item by item, and feedback will be obtained for each question. The interviewer will also record information regarding any questions received from physicians or other feedback indicating difficulty with any question or wording.

Cognitive pre-testing of the base language questionnaire (British English) will be completed first, and any updates to the questionnaire will be made before obtaining translations. After both forward- and back-translation, each local language questionnaire will be further reviewed by a native language speaker to align with the local language IMLYGIC PEB approved for each participating country, and for consistency with local medical standards.

9.4 Data Sources

Data will be collected primarily by on-line EDC. A paper-based survey may be offered as an alternative mode of survey completion depending on survey response rates.

Physicians who have completed the training required for HCPs as part of the IMLYGIC controlled distribution programme will be recruited. A list of such physicians from the 4 participating countries will be compiled using lists provided by Amgen obtained from the controlled distribution programme. Invitations to participate in the survey will be sent to up to 125 physicians by either email (preferred) or by post mail (if email is not available). The invitation letter will include information about the survey, a unique code, and instructions for accessing the survey. The unique code is used to protect physicians' confidentiality. The unique code will also be used to track who has already completed a survey so that reminders are only sent to physicians who have not yet completed the survey.

The survey is anticipated to be conducted over a maximum period of 7 months. For countries which take longer to complete required regulatory notifications and approvals, this period may be reduced. Depending on response rates, follow-up reminders will be sent to non-respondents. Metrics on survey participation will be tracked to monitor progress and to identify non-responders, who will receive follow-up reminders to complete the survey if less than the target number of completed surveys has been received. The maximum number of follow-up attempts per HCP will not exceed two.

9.5 Study Size

A sample of 30 to 50 completed physician surveys is targeted for this study. This sample size is determined based on both practical and statistical considerations, including the limited access and use of IMLYGIC in Europe, the controlled distribution programme which limits prescribing and injecting to specially trained HCPs, and the low response rate for surveys in general. The potential pool of eligible participants is approximately 125 physicians. Although participation has been reported in the literature to be as low as 0.5% in other survey studies evaluating the effectiveness of risk minimization measures (Agyemang et al, Pharm Med 2017), a higher response rate of 20-30% is projected because of the level of engagement of physicians within the controlled distribution programme, and based on ICON's anecdotal experience with HCP surveys for similar controlled distribution programmes, where response rates have ranged from 18-29%). Although all efforts will be made to reach the target, the actual sample size will depend on physicians' willingness to participate in the survey.

The primary evaluation criteria are the levels of physicians' knowledge of the key messages included in the IMLYGIC PEB. As such, the study sample size has been based on the primary endpoint. Table 1 provides the precision and two-sided 95% confidence interval (CI) around expected knowledge levels by various numbers of completed surveys for this study. A sample size of 50 HCP respondents allows estimation of a minimum HCP knowledge level of at least 80% with a precision of 11.9% (Table 1).

Table 1. Precision and 95% Confidence Intervals for Various Combinations of Sample Size and Knowledge Rates

Sample Size	Probable Rates of Respondent Knowledge							
	60%		70%		80%		90%	
	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI
20	21.5	38.5-81.5	20.1	49.9-90.10	17.5	62.5-97.5	11.6	76.9-100.0
30	17.5	42.5-77.5	16.4	53.6-86.4	14.3	65.7-94.3	10.4	79.3-100.0
40	15.2	44.8-75.2	14.2	55.8-84.2	12.4	67.6-92.4	9.3	80.7-99.3
50	13.6	46.4-73.6	12.7	57.3-82.7	11.1	68.9-91.1	8.3	81.7-98.3

Note: Calculated using PASS 13 software, * confidence intervals for 1 proportion, simple asymptotic formula (Hintze J, 2014).

9.6 Data Management

Survey data collection will be completed in a suitable software platform for the creation and delivery of surveys. Data collected will be stored on secure servers and will be maintained to ensure compliance with applicable local or national regulations.

Response sets for all multiple-choice questions will be randomised to minimise bias. To minimise likelihood that respondents would look up answers and/or discuss the survey while taking it, respondents will be asked to complete survey in one sitting and will not be allowed to revise their answers after they advance to the next question.

Survey database lock is anticipated to occur shortly after the survey is closed. To reduce opportunity for bias, survey respondents will not be contacted to clarify or revise their responses.

Additional details regarding data collection, management of missing data, data storage, and validation procedures will be detailed in the survey manual and statistical analysis plan (SAP).

Data management will be in accordance with the standard operating procedures (SOPs) of ICON.

9.6.1 Obtaining Data Files

Not applicable. This study involves primary data collection and will not use data from existing databases.

9.6.2 Linking Data Files

Not applicable. This study involves primary data collection and will not use data from existing databases; therefore, no linkage is required.

9.6.3 Review and Verification of Data Quality

This study will evaluate physicians' knowledge of safety messages included in the PEB for IMLYGIC. To reduce opportunity for bias, survey respondents will not be contacted to clarify or revise their responses.

9.7 Data Analysis

Statistical analyses will be descriptive. A SAP will be developed and will describe all planned analyses in detail, along with any specifications for tables, listings, and figures to be produced. All analyses will be performed using appropriate statistical software (eg, SAS® Version 9.0 or later). A report summarising the results of the survey will be developed.

9.7.1 Planned Analyses

9.7.1.1 Primary Analysis

The primary analysis will be performed at a single time point after the survey database has been closed.

The primary analysis population will include all physicians who have completed at least 1 of the endpoint questions in the survey. Denominators used to calculate knowledge levels for individual survey questions will reflect the number of respondents who completed each individual survey question including responses of 'don't know/not sure'.

The primary outcome are knowledge levels of the key messages conveyed in the IMLYGIC PEB (risk of disseminated herpetic infection in immunocompromised individuals, risk of accidental exposure or transmission of IMLYGIC to close contacts or HCPs, risk of symptomatic herpetic infection due to latency and reactivation of IMLYGIC or wildtype herpes in patients, IMLYGIC use in pregnancy, safe use and handling of IMYLIGIC, and important accompanying patient materials). Success criteria for the primary outcome is defined as at least 80% of physicians provide a correct response to each individual knowledge-related question (as described in section 9.3.2) that has a minimum n = 30.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

Descriptive data analyses will be conducted. Descriptive statistics for continuous data will include N, means, and standard deviations. Results for some continuous variables may include ranges (minimums and maximums) and medians as well. Categorical data will be summarised using frequency counts and percentages. Levels of receipt, reading, and knowledge will be calculated with 95% two-sided CI and will be reported overall and by country.

Data analysis will be performed by ICON in accordance with ICON's SOPs for statistical programming.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing data will be reviewed solely for the purposes of deriving the endpoints. No replacement or imputation will be performed. Descriptive statistics for continuous variables will include the available n, and descriptive statistics for categorical variables will include a category of "missing" when applicable.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

The following variables will be described, overall and by country:

- Survey status
    - Number and percentage of surveys with eligibility questions completed
    - Number and percentage of surveys with all, and partial, completion of the primary and secondary effectiveness endpoint questions
- Eligibility (Yes/No)
    - If No, reasons for exclusion (ie, number and percentage of physicians who do not meet each specific eligibility criteria)
    - Primary analysis set (number and percentage of physicians in the primary analysis *set*)

9.7.2.3.2 Description of Physician Characteristics

Frequencies and percentages will be used to summarise the distribution of physicians' characteristics, including missing responses, for the primary analysis set overall, and by country.

Frequencies and percentages will be used to briefly summarise the characteristics of physicians who responded vs. did not respond to the survey (eg, response rates by

country) based on information available in the controlled distribution programme's HCP list of trained sites.

9.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

Frequencies, percentages, and corresponding 95% CIs will be used to summarise the endpoints for the primary analysis set overall, by country, and by subgroups. For each knowledge-related question, the percentage of HCPs who provide correct answers to each question will be estimated and assessed against the 80% (± 95% CI) target for questions where the minimum n = 30. For secondary endpoints of receipt and reading of the PEB, and distribution of patient-directed materials, percentages and 95% CI will be estimated.

Frequencies and percentages will be used to summarise the distribution of all response choices, including missing responses, for all single questions regarding receipt, reading, and knowledge of the information included in the IMLYGIC PEB. This will be performed for the primary analysis set overall and by country.

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

All analyses will be performed overall and by country.

In addition, the primary analysis will be performed overall, and may be stratified by the following subgroups, if there are at least 10 HCPs in each applicable subgroup: practice setting, primary medical **specialty**, and IMLYGIC prescribing status.

9.7.2.5.2 Other Sensitivity Analysis

The primary analysis will be performed by having read (all or some) vs. not read (no or don't know/not sure) the IMLYGIC PEB. An analysis to evaluate the impact of recall bias will be performed by repeating the primary analysis stratified by tertiles of time since physicians completing the required IMLYGIC training.

9.8 Quality Control

SOPs will be followed where appropriate to ensure data quality and integrity, including archival of statistical programs, documentation of data cleaning, and validation of derived variables and analyses.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

This study will evaluate physicians' knowledge of safety messages included in the PEB for IMLYGIC. However, information included in the PEB is also available from other

sources such as the IMLYGIC SmPC. Therefore, it may not be possible to attribute the study results solely to the effectiveness of the PEB.

Since surveys rely on self-reporting, this can result in social desirability reporting bias, where reports of actions or behaviour may be biased towards positive values. However, the impact of social desirability reporting bias may be low. In a web-based survey of 3625 HCPs across 9 EU countries conducted under the Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) joint action initiative, a range of 28% to 97% of HCPs reported receiving and sometimes reading risk communication materials, suggesting HCPs may be comfortable giving a truthful response (even if possible "socially undesirable") to this type of question (Montero, 2016; van der Sar *et al.*, 2016).

Recall bias is an inherent limitation when assessing knowledge levels, especially if there is a long lag time between exposure to educational material and assessment of knowledge. The impact of recall bias will be assessed by evaluating the time since HCPs' completed the required IMLYGIC training to when they completed the survey.

Measures to minimise information bias for this study are:

- Response sets for all multiple-choice questions are randomised (on-line surveys only),
- Physicians are instructed to complete the survey in 1 sitting (to minimise the likelihood of looking up the correct answers),
- Questions must be answered in sequence (on-line surveys only),
- Responses cannot be changed once submitted (going back to change previously answered questions is not permitted in the on-line survey), and
- Physicians who complete a survey will not be contacted to clarify or revise their survey responses.

9.9.2 External Validity of Study Design

A primary limitation of a cross-sectional survey is selection bias due low response rates. The impact of selection bias can be minimised through robust outreach to recruit all eligible HCPs who have been trained in the controlled distribution programme and prescribed IMLYGIC in Europe. To minimise selection bias for this survey, physicians from Austria, Germany, Netherlands, and the UK will be invited to participate. Participants will receive up to 2 reminders to encourage their participation. These countries were selected to enable a representative sample of the European countries where IMLYGIC is reimbursed. Specifically, countries with the largest use of IMLYGIC were selected to ensure a reasonable number of physicians who prescribe IMLYGIC will

be available to recruit. This was the primary factor driving country selection for this study. After considering market share, a variety of countries to ensure reasonable geographic representation as well as study feasibility was considered.

Generalisability of the study results may be limited if the physicians who participate in the study are different from those who do not participate. However, all physicians in the 4 participating countries who have completed the required IMLYGIC training and have ordered IMLYGIC will be invited to participate in the survey. Analysis Limitations

This study will endeavor to collect 30 to 50 completed physician surveys. From a statistical perspective, this sample size is small, and therefore, estimates of knowledge levels may lack precision.

10. Protection of Human Subjects

10.1 Informed Consent

Physician consent will be obtained prior to completing the survey questionnaire. Physicians who decline to provide their consent will be unable to complete the survey.

10.2 Institutional Review Board/Independent Ethics Committee

Local approvals from ethics committees are not required for knowledge assessment surveys conducted in the 4 participating countries, as no clinical data regarding patients or HCPs will be collected.

10.3 HCP Confidentiality

To maintain confidentiality, a unique numeric code will be assigned to each physician. This unique code will be entered in the study-specific survey database and only the study vendor will have access to the link between the physician's unique code and their identity.

Physicians who wish to receive the FMV payment for completing the survey will have the option to enter their electronic payment transfer details into the study-specific database. Only the study vendor will have access to the electronic payment transfer details.

Physician personal data, including electronic payment transfer details, will be treated in compliance with the General Data Protection Regulation and all applicable local laws and regulations.

10.4 Subjects Decision to Withdraw

Physicians have the right to withdraw from the study at any time and for any reason without prejudice to their future participation in an Amgen-sponsored study or their ability to prescribe IMLYGIC.

Withdrawal of consent for a study means that the physician does not wish to or is unable to continue further study participation. If requested by a physician, their survey responses can be removed from the analysis database and not used in the final study report. Amgen will provide physicians with information regarding appropriate steps for withdrawal of their consent from the study.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints

This study is collecting information from HCPs via a survey conducted at a single timepoint to assess HCPs' knowledge of safety messages included in the PEB for IMLYGIC. The survey does not involve collection of any patient-specific outcomes nor does it include questions intended to identify safety events (adverse events, product complaints, and other safety findings). However, it is possible that HCPs' may report a safety event during conduct of the survey (eg, in an open text field in the on-line survey questionnaire or in the margin of a paper survey questionnaire).

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the HCP's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the *patient* at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is an "other medically important serious event" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other medically important serious events" refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

- Talimogene Laherparepvec

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from healthcare professionals using questionnaires at a single time point. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to IMLYGIC will

be collected if reported at time of survey. ICON is responsible for ensuring that all safety events they become aware of during study period are recorded in the patient's appropriate study documentation. Those safety events which are considered serious must also be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of ICON's awareness. Non-serious Adverse Events (AEs) must be reported in an expeditious manner, not to exceed 15 calendars days of ICON's awareness.

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix E for sample Pregnancy and Lactation Notification Worksheets. The HCP may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The HCP is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, competent authority notifications must be completed where applicable per local governing law and/or regulations. The independent ethics committee (IEC) must be informed of all amendments and give approval if applicable.

Amgen reserves the right to terminate the study at any time. If applicable, Amgen is to notify the IEC in writing of the study's completion or early termination.

13. Plans for Disseminating and Communicating Study Results

The protocol and an abstract of results will be posted as per guidelines for studies meeting the criteria for PASS. The results of this study will be submitted for publication.

13.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

1. Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. Compensation

Physicians will be compensated with **an** FMV payment for the time and effort spent to complete the survey. The amount of the FMV payment will be based on an assessment of the time and effort to complete the survey and will follow local FMV payment laws and/or guidelines as applicable in each participating country.

15. References

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16. Appendices

Appendix A. List of Stand-alone Documents

No.	Title
1	*Questionnaire for Healthcare Professionals who Prescribe or Inject IMLYGIC*

Appendix B. ENCePP Checklist for Study Protocols

20180099 ENCePP
Checklist for Study F

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A Cross-sectional Survey to Evaluate Physician Knowledge of Safety Messages Included in the Physician Education Booklet (PEB) for IMLYGIC®

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.1, 11.2

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2, 9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	9.1, 9.2
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?	☐	☐	☒	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.4

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.4
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.1, 8.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.4
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	

Section 7: Bias	Yes	No	N/A	Section Number
7.2 Does the protocol address:	☒	☐	☐	9.9
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	9.3.3

Comments:

Section 8: Effect modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2, 9.4
9.1.3 Covariates?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2, 9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3.
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7.2.5.1
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2, 9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD, PhD, MPH

Date: 19/September/2018

Signature: PPD

Appendix C. Sample Safety Reporting Form(s)

20180099. Safety reporting form_2.pd

Observational Research Safety Reporting Form Instructions

This form is for use for observational studies that are using paper report form

General Instructions

The protocol will provide instruction on what types of events to report for the study. *Indicates a mandatory field.

What to report on this form:

- **All adverse events (AEs) are associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol.**
- **The following safety findings are to be reported on this form as events regardless of association with an AE:**
  - **medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product**
  - **transmission of infectious agents**
  - **reports of uses outside the terms for authorized use of the product including off label use**
  - **occupational exposure**
  - **any lack or loss of intended effect of the product(s)**
  - **product complaint (PC)**
  - **adverse device effect (ADE)**

The following should not be reported on this form and should be reported via the normal process set up for the study

- **pregnancy and lactation reports**

1. **Initial or Follow-up*** – Please tick the appropriate box
2. **Site Number* –** Enter your assigned site number for this study. **Subject Number* –** Enter the entire number assigned to the subject.
3. **Indicate event type* –** Tick the relevant box which applies to the event(s) you are reporting. Please note, more than one box can be ticked.
4. **Contact Details* –** Provide your name, phone, address, etc. (These contact details should be for the Vendor or Investigator)
5. **Reporter ID* –** Provide name or ID of reporter, phone, address, etc. (This could be the Investigator details if vendor details are added in section 4.
6. **HCP Contact Details (if other than reporter)* –** Provide name or ID of reporter, country, phone, address, etc.
7. **Patient* –** Enter the subjects demographic information.
8. **Medical History (include primary diagnosis)* –** Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event, allergies and any relevant prior therapy, such as radiation. Include dates if available.
9. **Suspect Product Information (include dosing details)* –** Provide Product/Device information, Indication, start date, stop date, dose, route, frequency, Lot#, Serial#. It is important that all efforts are taken to provide the Lot number, were possible.
10. **AE, Other Safety Finding, PC/ADE Information*:**

AE Diagnosis or Syndrome*:

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

Onset Date* – Enter date the AE first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

Resolved Date* – Enter date the AE ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

Hospitalization* – If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regard less of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an AE. Protocol specified hospitalizations are exempt.

Serious Criteria Code* – This is a mandatory field for serious events. Select the appropriate code for the event(s) being reported

Action Taken* – State what action has been taken with suspect drug/device.

Outcome* – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

Severity* – State the severity of the safety event being reported.

Relationship to Product/Device*:

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported.

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g., prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g., heating pads, infusion pumps)**

11. **Concomitant Medications* –** Indicate if there are any medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is co-suspect in the event.

Continuing – Indicate if the subject is still taking the medication.

Event Treatment – Indicate if the medication was used to treat the event.

12. **Relevant Laboratory Tests* –** Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

13. **Other Relevant Tests* –** Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results, and units (if applicable).

14. **Description* –** Describe Event.

Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of each page and fax the form to Amgen.

Project ID: 20180099	AMGEN	**Observational Research Safety Reporting Form**	Date of Reporter Awareness:
			Date Reported to Amgen:
	Fax reports to: Amgen Local Office	*<<populate LAO fax here or delete language>>*	

1. **Initial:** ☐ **Follow-up:** ☐

2. **Site Number:** **Subject Number:**

3. **Indicate event type:** ***(Please tick all that apply)*** ☐ **AE/Other Safety Finding** ☐ **Product Complaint (PC)** ☐ **Adverse Device Effect (ADE)**

4. Contact Details (Vendor/Investigator)

Name	*Phone*	*Fax*
Address		
City	*State/Province*	
Postal Code	*Country*	

5. Reporter ID

Name or ID	*Phone*	*Fax*
Address		
City	*State/Province*	
Postal Code	*Country*	

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	*State/Province*	*Postal Code*
Phone	*Fax*	

7. Patient

Initials (optional)	*Sex*	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?*
	☐ F ☐ M		☐ Yes ☐ No

Weight	*Height*	*Race*	*Is patient also reporter?*
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

8. Medical History (include primary diagnosis)

9. Suspect Product Information (include dosing details)

Product/Device: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	**Onset Date** (day month year)	**Resolved Date** (If patient died, list date of death) **Cause of Death:** (provide autopsy report) (day month year)	**Hospitalization** Hospitalized? ☐ Yes ☐ No Prolonged Hospitalization? ☐ Yes ☐ No Admitting dx _____ Date Admitted (day month year)	Date Discharged (day month year)	**Serious Criteria** 01 Fatal 02 Immediately life-threatening 03 Required/Prolonged hospitalization 04 Persistent or significant disability /incapacity 05 Congenital anomaly/birth defect 06 Other significant medical hazard 07 Non serious	**Action Taken** 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=drug rechallenge (state outcome)	**Outcome** 01 Recovered/ Resolved 02 Recovering/ Resolving 03 Not recovered/not resolved 04 Recovered/ resolved with sequelae 05 Fatal 06 Unknown	**Severity** 1=mild 2=moderate 3=severe	**Relationship to Product/Device** Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

Reporter Signature: _____ **Page 3 of** _____

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	 Yes	Continuing No	 Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

The latest version of the Common Terminology Criteria for Adverse Events (CTCAE) should be used. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix E. Pregnancy and Lactation Notification Worksheets


20180099. Pregnancy notificati


20180099. Lactation notification form.pd

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180099

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐ Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180099

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Appendix F. Physician Education Booklet

Imlygic Information for Physician.pdf

Physician Education Booklet.pdf

Imlygic® Information for Physicians: Risks of Transmission and Herpetic Complications, and Safe Use and Handling of Imlygic®

This Physician Education Brochure is to inform you of:

- **the risks of disseminated herpetic infection in immunocompromised individuals**
- **herpetic infection in treated patients**
- **accidental exposure of healthcare professionals and close contacts to Imlygic®**
- **Imlygic® use in pregnancy**
- **information on safe use and handling of Imlygic®**
- **important accompanying patient materials**

This brochure does not contain a comprehensive description of the risks associated with Imlygic®. Please read the current Summary of Product Characteristics (SmPC) for Imlygic®.

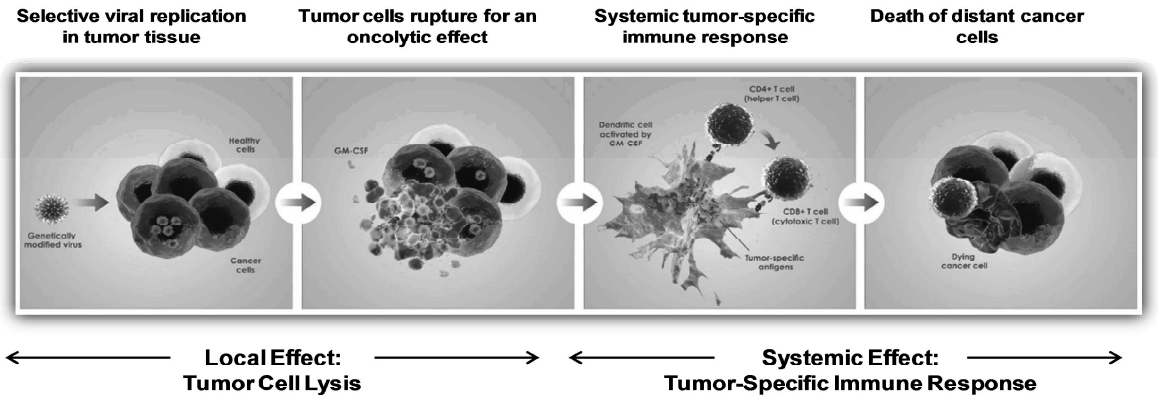
Imlygic® is an attenuated herpes simplex virus type 1 (HSV-1) derived by functional deletion of 2 genes (ICP34.5 and ICP47) and insertion of coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF). Imlygic® is produced in Vero cells by recombinant DNA technology.

Imlygic® is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease (see SmPC section 4.4 and 5.1).

Imlygic® Mechanism of Action

Imlygic® is an oncolytic immunotherapy that is derived from HSV-1. Imlygic® has been modified to efficiently replicate within tumours and to produce the immune stimulatory protein human GM-CSF. Imlygic® causes lytic tumour cell death and release of tumour-derived antigens and GM-CSF, which together promote a systemic anti-tumour immune response.

The modifications to Imlygic® from HSV-1 include deletion of ICP34.5 and ICP47. Deletion of ICP34.5 allows Imlygic® replication in tumour tissue; normal cells are able to protect against Imlygic® infection as they contain intact anti-viral defense mechanisms. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of HSV US11 gene, which enhances viral replication in tumour cells. GM-CSF recruits and activates antigen presenting cells which can process and present tumour-derived antigens to promote an effector T-cell response.



Important Risks and Precautions

Disseminated Herpetic Infection in Immunocompromised Individuals

- Imlygic® is contraindicated in severely immunocompromised individuals. Based on animal data, patients who are severely immunocompromised (patients with any severe congenital or acquired cellular and/or humoral immune deficiency) are at risk of developing life-threatening disseminated herpetic infection and should not be treated with Imlygic®.
- Consider the risks and benefits of treatment before administering Imlygic® to immunocompromised patients e.g. those with:
    - HIV/AIDS
    - leukemia, lymphoma
    - common variable immunodeficiency
    - those who require chronic high dose steroids or other immunosuppressive agents (eg, chemotherapy)
- Immunocompromised healthcare professionals, including pregnant women, should not prepare or administer Imlygic®.
- Close contacts who are immunocompromised should not change the patient's dressings or clean their injection sites.

Herpetic Infection in Treated Patients

Herpetic infections including cold sores and herpes keratitis have been reported in patients treated with Imlygic® in clinical studies. Patients who develop herpetic infections should be advised to follow standard hygiene practices to prevent viral transmission.

- Imlygic® is sensitive to acyclovir.
- Consider the risks and benefits of Imlygic® treatment before administering acyclovir or other anti-viral agents indicated for the management of herpetic infection. These agents may interfere with the effectiveness of Imlygic®.

Accidental Exposure and Transmission of Imlygic® to Healthcare Professionals

Accidental exposure to Imlygic® may lead to transmission of Imlygic® and herpetic infection. It is important to follow the precautions below to avoid accidental exposure to Imlygic®.

- Always wear protective gown or laboratory coat, safety glasses, and gloves while preparing or administering Imlygic®.
- Cover any exposed wounds before handling Imlygic®.
- Avoid contact with skin, eyes, or mucous membranes.
- Avoid ungloved direct contact with injected lesions or body fluids of treated patients.

- Accidental needle-stick and splash-back into eyes or mouth have been reported in healthcare professionals during preparation and administration of Imlygic®.
- In the event of accidental exposure to the eyes or mucous membranes, flush with clean water for at least 15 minutes.
- In the event of exposure to broken skin or needle stick, exposed individuals should be advised to clean the affected area thoroughly with soap and water and/or a disinfectant.
- Imlygic® is sensitive to acyclovir.

Accidental Exposure and Transmission of Imlygic® to Close Contacts

Accidental exposure to Imlygic® may lead to transmission of Imlygic® and herpetic infection. The following precautions should be followed to avoid accidental exposure and prevent transmission of Imlygic® to close contacts (household members, caregivers, sex partners, or someone the patient shares a bed with) of treated patients:

- After administration, change gloves prior to applying occlusive dressings to injected lesions. Wipe the exterior of occlusive dressing with an alcohol wipe. Advise patients to keep the injection sites covered with airtight and watertight dressings at all times, if possible. To minimize the risk of viral transmission, patients should keep their injection sites covered for at least 8 days from the last treatment visit or longer if the injection site is weeping or oozing. Patients should be advised to keep the dressing on until the weeping or oozing resolves. Advise patients to apply the dressing as instructed by their healthcare provider and to replace the dressing if it falls off.
- Patients should be advised to follow standard hygiene practices to prevent viral transmission to close contacts.
- Close contacts should avoid direct contact with injected lesions or body fluids of treated patients.
    - The treated patient should minimize the risk of exposure of blood and body fluids to close contacts for the duration of Imlygic® treatment through 30 days after the last administration of Imlygic®. The following activities should be avoided:
        - Sexual intercourse without a latex condom
        - Kissing if either party has an open mouth sore
        - Common usage of cutlery, crockery, and drinking vessels
        - Common usage of injection needles, razorblades, and toothbrushes
- Caregivers should be advised to wear protective gloves when assisting patients in applying or changing occlusive dressings and to observe safety precautions for disposal of used dressings and cleaning materials.
    - Treat all Imlygic® spills with a virucidal agent and absorbent materials.
    - Advise patients to place used dressings and cleaning materials in a sealed plastic bag and dispose as household waste.
- If close contacts come in contact with the injection site or body fluids they should be advised to clean the affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, they should contact their healthcare professional.
- Imlygic® is sensitive to acyclovir.

Suspected herpetic lesions

For suspected herpetic lesions, a laboratory test may be performed at the discretion of the treating physician for a polymerase chain reaction (PCR) test for DNA specific to Imlygic®.

For further information on testing of suspected herpetic lesions, please contact the local Amgen representative at {insert local medical information number}.

Pregnancy

- Adequate and well controlled studies have not been conducted in pregnant women.
- No effects on embryo-fetal development have been reported in animal studies.
- Wild-type herpes simplex virus type-1 (HSV-1) infection in the mother has been associated with life-threatening or fatal disseminated herpetic infection in the fetus or neonate in pregnancy or during birth due to viral shedding. There could be a risk to the fetus or neonate if Imlygic® were to act in the same manner.
- Transplacental metastases of malignant melanoma can occur. Because Imlygic® is designed to enter and replicate in the tumour tissue, there could be a risk of foetal exposure to Imlygic® from tumour tissue that has crossed the placenta.
- Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with Imlygic®.
- Advise patients of the potential hazards to the fetus and/or neonate if Imlygic® is used during pregnancy or if the patient becomes pregnant while taking Imlygic®

Important Accompanying Patient Materials

Please review this important safety information with your patients every time you administer Imlygic®:

- Package Leaflet - includes important safety information for patients receiving Imlygic®
- Patient Safety Brochure – a brief summary of the risks of accidental exposure and transmission of Imlygic®, risk in immunocompromised individuals, measures for safe use and prevention of accidental exposure, and what to do if a close contact is accidentally exposed to Imlygic®
- Please ensure the patients receive the completed Patient Alert Card with the first administration of Imlygic®. Record the batch number for every administration of Imlygic® on the Patient Alert Card. Patients should be instructed to carry the Alert Card with them at all times and present it to healthcare professionals upon consultation or hospitalization.
- At subsequent Imlygic® administrations, please ensure the patient has not lost the Alert Card and supply a new one if needed.

Amgen requests that you provide each patient with a Package Leaflet and Patient Safety Brochure every time you administer Imlygic® to your patients as the information contained within may change over time. Copies are enclosed for your reference.

Reporting of Adverse Reactions:

Imlygic® is classified as an Advanced Therapy Medicinal Product, and therefore you are requested to provide the manufacturing batch number when reporting suspected adverse reactions.

- A peelable label is provided with each vial of Imlygic®. Please affix the peelable label with the batch number onto the patient's medical record for each injection administered.
- Always provide the batch number from the patient's record when reporting suspected adverse reactions.

Please refer to the current Summary of Product Characteristics (SmPC) for Imlygic® {insert local CA repository or EMA website}. Should you have any questions or require additional information regarding the use of Imlygic®, please contact Amgen Medical Information on *(insert local contact).*

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for information on the reporting of suspected adverse reactions

References: 1. Imlygic® Draft Summary of Product Characteristics. 2.Varghese S, et al. *Cancer Gene Ther.* 2002;9:967-978. 3.. Hawkins LK, et al. *Lancet Oncol.* 2002;3:17-26. 4. Fukuhara H, et al. *Curr Cancer Drug Targets.* 2007;7:149-155. 4. Sobol PT, et al. . *Mol Ther.* 2011;19:335-344. 6. Liu BL, et al. *Gene Ther.* 2003;10:292-303. 7. Melcher A, et al. *Mol Ther.* 2011;19:1008-1016. 8. Fagoaga OR In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods, 22nd ed. Philadelphia, PA: Elsevier; 2011:933-953. 9. Dranoff G. *Oncogene.* 2003;22:3188-3192.

IMPORTANT RISKS AND PRECAUTIONS

IMPORTANT ACCOMPANYING PATIENT MATERIALS

Please review this important safety information with your patients every time you administer IMLYGIC®:

- Package Leaflet – includes important safety information for patients receiving IMLYGIC®.
- Patient Safety Brochure – a brief summary of the risks of accidental exposure and transmission of IMLYGIC®, risk in immunocompromised individuals, measures for safe use and prevention of accidental exposure, and what to do if a close contact is accidentally exposed to IMLYGIC®.
- Please ensure the patients receive the completed Patient Alert Card with the first administration of IMLYGIC®. Record the batch number for every administration of IMLYGIC® on the Patient Alert Card. Patients should be instructed to carry the Alert Card with them at all times and present it to healthcare professionals upon consultation or hospitalisation.
- At subsequent IMLYGIC® administrations, please ensure the patient has not lost the Alert Card and supply a new one if needed.

Amgen requests that you provide each patient with a Package Leaflet and Patient Safety Brochure every time you administer IMLYGIC® to your patients as the information contained within may change over time. Copies are enclosed for your reference.

REPORTING OF ADVERSE REACTIONS

IMLYGIC® is classified as an Advanced Therapy Medicinal Product, and therefore you are requested to provide the manufacturing batch number when reporting suspected adverse reactions.

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- Always provide the batch number from the patient's record when reporting suspected adverse reactions.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for information on the reporting of suspected adverse reactions.

PLEASE REFER TO THE CURRENT SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) FOR IMLYGIC® {INSERT LOCAL CA REPOSITORY OR EMA WEBSITE}.

SHOULD YOU HAVE ANY QUESTIONS OR REQUIRE ADDITIONAL INFORMATION REGARDING THE USE OF IMLYGIC®, PLEASE CONTACT AMGEN MEDICAL INFORMATION ON {INSERT LOCAL CONTACT}.

REFERENCES:
1. IMLYGIC® Draft Summary of Product Characteristics. **2.** Varghese S, *et al.* Cancer Gene Ther. 2002;9:967-978. **3.** Hawkins LK, *et al.* Lancet Oncol. 2002;3:17-26. **4.** Fukuhara H, *et al.* Curr Cancer Drug Targets. 2007;7:149-155. **5.** Sobol PT, *et al.* Mol Ther. 2011;19:335-344. **6.** Liu BL, *et al.* Gene Ther. 2003;10:292-303. **7.** Melcher A, *et al.* Mol Ther. 2011;19:1008-1016. **8.** Fagoaga OR In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods, 22nd ed. Philadelphia, PA: Elsevier; 2011:933-953. **9.** Dranoff G. Oncogene. 2003;22:3188-3192.

RISKS OF TRANSMISSION AND HERPETIC COMPLICATIONS, AND SAFE USE AND HANDLING OF IMLYGIC®

THIS PHYSICIAN EDUCATION BROCHURE IS TO INFORM YOU OF:

the risks of disseminated herpetic infection in immunocompromised individuals	**herpetic infection in treated patients**
accidental exposure of healthcare professionals and close contacts to IMLYGIC®	**IMLYGIC® use in pregnancy**
information on safe use and handling of IMLYGIC®	**important accompanying patient materials**

This brochure does not contain a comprehensive description of the risks associated with IMLYGIC®. Please read the current Summary of Product Characteristics (SmPC) for IMLYGIC®.

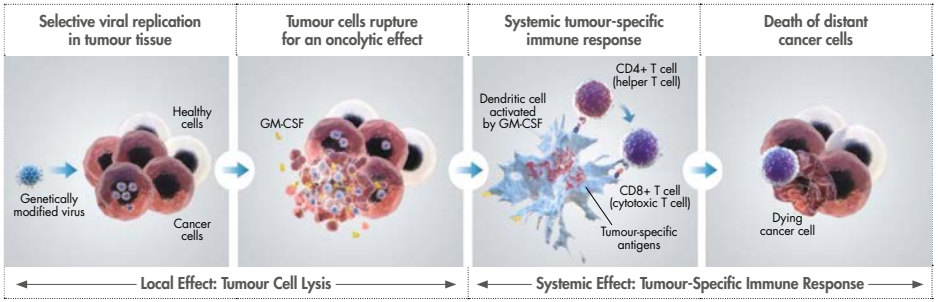
IMLYGIC® is an attenuated herpes simplex virus type 1 (HSV-1) derived by functional deletion of 2 genes (ICP34.5 and ICP47) and insertion of coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF). IMLYGIC® is produced in Vero cells by recombinant DNA technology.

IMLYGIC® is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease (see SmPC sections 4.4 and 5.1).

IMLYGIC® MECHANISM OF ACTION

IMLYGIC® is an oncolytic immunotherapy that is derived from HSV-1. IMLYGIC® has been modified to efficiently replicate within tumours and to produce the immune stimulatory protein human GM-CSF. IMLYGIC® causes lytic tumour cell death and release of tumour-derived antigens and GM-CSF, which together promote a systemic anti-tumour immune response.

The modifications to IMLYGIC® from HSV-1 include deletion of ICP34.5 and ICP47. Deletion of ICP34.5 allows IMLYGIC® replication in tumour tissue; normal cells are able to protect against IMLYGIC® infection as they contain intact anti-viral defense mechanisms. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of HSV US11 gene, which enhances viral replication in tumour cells. GM-CSF recruits and activates antigen presenting cells which can process and present tumour-derived antigens to promote an effector T-cell response.



DISSEMINATED HERPETIC INFECTION IN IMMUNOCOMPROMISED INDIVIDUALS

- IMLYGIC® is contraindicated in severely immunocompromised individuals. Based on animal data, patients who are severely immunocompromised (patients with any severe congenital or acquired cellular and/or humoral immune deficiency) are at risk of developing life-threatening disseminated herpetic infection and should not be treated with IMLYGIC®.
- Consider the risks and benefits of treatment before administering IMLYGIC® to immunocompromised patients e.g. those with:
  - HIV/AIDS
  - leukaemia, lymphoma
  - common variable immunodeficiency
  - those who require chronic high dose steroids or other immunosuppressive agents (e.g. chemotherapy)
- Immunocompromised healthcare professionals, including pregnant women, should not prepare or administer IMLYGIC®.
- Close contacts who are immunocompromised should not change the patient's dressings or clean their injection sites.

HERPETIC INFECTION IN TREATED PATIENTS

Herpetic infections including cold sores and herpes keratitis have been reported in patients treated with IMLYGIC® in clinical studies. Patients who develop herpetic infections should be advised to follow standard hygiene practices to prevent viral transmission.

- IMLYGIC® is sensitive to acyclovir.
- Consider the risks and benefits of IMLYGIC® treatment before administering acyclovir or other anti-viral agents indicated for the management of herpetic infection. These agents may interfere with the effectiveness of IMLYGIC®.

ACCIDENTAL EXPOSURE AND TRANSMISSION OF IMLYGIC® TO HEALTHCARE PROFESSIONALS

Accidental exposure to IMLYGIC® may lead to transmission of IMLYGIC® and herpetic infection. It is important to follow the precautions below to avoid accidental exposure to IMLYGIC®.

- Always wear protective gown or laboratory coat, safety glasses and gloves while preparing or administering IMLYGIC®.
- Cover any exposed wounds before handling IMLYGIC®.
- Avoid contact with skin, eyes, or mucous membranes.
- Avoid ungloved direct contact with injected lesions or body fluids of treated patients.
- Accidental needle-stick and splash-back into eyes or mouth have been reported in healthcare professionals during preparation and administration of IMLYGIC®.
- In the event of accidental exposure to the eyes or mucous membranes, flush with clean water for at least 15 minutes.
- In the event of exposure to broken skin or needle stick, exposed individuals should be advised to clean the affected area thoroughly with soap and water and/or a disinfectant.
- IMLYGIC® is sensitive to acyclovir.

ACCIDENTAL EXPOSURE AND TRANSMISSION OF IMLYGIC® TO CLOSE CONTACTS

Accidental exposure to IMLYGIC® may lead to transmission of IMLYGIC® and herpetic infection. The following precautions should be followed to avoid accidental exposure and prevent transmission of IMLYGIC® to close contacts (household members, caregivers, sex partners, or someone the patient shares a bed with) of treated patients:

- After administration, change gloves prior to applying occlusive dressings to injected lesions. Wipe the exterior of occlusive dressing with an alcohol wipe. Advise patients to keep the injection sites covered with airtight and watertight dressings at all times, if possible. To minimize the risk of viral transmission, patients should keep their injection sites covered for at least 8 days from the last treatment visit or longer if the injection site is weeping or oozing. Patients should be advised to keep the dressing on until the weeping or oozing resolves. Advise patients to apply the dressing as instructed by their healthcare provider and to replace the dressing if it falls off.
- Patients should be advised to follow standard hygiene practices to prevent viral transmission to close contacts.
- Close contacts should avoid direct contact with injected lesions or body fluids of treated patients.
  - The treated patient should minimize the risk of exposure of blood and body fluids to close contacts for the duration of IMLYGIC® treatment through 30 days after the last administration of IMLYGIC®. The following activities should be avoided:
    - Sexual intercourse without a latex condom
    - Kissing if either party has an open mouth sore
    - Common usage of cutlery, crockery, and drinking vessels
    - Common usage of injection needles, razorblades, and toothbrushes
- Caregivers should be advised to wear protective gloves when assisting patients in applying or changing occlusive dressings and to observe safety precautions for disposal of used dressings and cleaning materials.
  - Treat all IMLYGIC® spills with a virucidal agent and absorbent materials.
  - Advise patients to place used dressings and cleaning materials in a sealed plastic bag and dispose as household waste.
- If close contacts come in contact with the injection site or body fluids they should be advised to clean the affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, they should contact their healthcare professional.
- IMLYGIC® is sensitive to acyclovir.

SUSPECTED HERPETIC LESIONS

For suspected herpetic lesions, a laboratory test may be performed at the discretion of the treating physician for a polymerase chain reaction (PCR) test for DNA specific to IMLYGIC®.

For further information on testing of suspected herpetic lesions, please contact the local Amgen representative at {insert local medical information number}.

PREGNANCY

- Adequate and well controlled studies have not been conducted in pregnant women.
- No effects on embryo-fœtal development have been reported in animal studies.
- Wild-type herpes simplex virus type-1 (HSV-1) infection in the mother has been associated with life-threatening or fatal disseminated herpetic infection in the fœtus or neonate in pregnancy or during birth due to viral shedding. There could be a risk to the fœtus or neonate if IMLYGIC® were to act in the same manner.
- Transplacental metastases of malignant melanoma can occur. Because IMLYGIC® is designed to enter and replicate in the tumour tissue, there could be a risk of foetal exposure to IMLYGIC® from tumour tissue that has crossed the placenta.
- Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with IMLYGIC®.
- Advise patients of the potential hazards to the fœtus and/or neonate if IMLYGIC® is used during pregnancy or if the patient becomes pregnant while taking IMLYGIC®.

Superseding Amendment 3, version 1.0

Protocol Title: A Cross-sectional Survey to Evaluate Physician Knowledge of Safety Messages Included in the Physician Education Booklet (PEB) for IMLYGIC®

Amgen Protocol Number 20180099

Amendment Date: 14 October 2019

Rationale:

The final CHMP assessment for Procedure No. EMEA/H/C/002771OO/0034 was received on 19 September 2019 and concludes that the 20180099 Protocol has sufficiently described the rationale for performing the study to evaluate the effectiveness of the patient-directed aRMMs. The survey questionnaire for physicians is considered comprehensive. No further action is required. This Superseding Amendment 3, version 1.0, is being submitted to seek full approval from ORRG.

In addition, this Superseding Amendment 3, version 1.0 is being submitted to correct for minor administrative changes.

- Inclusion of EU PAS Registry Number: EUPAS31188
- Appendix A: Imlgyic Physician Survey Questionnaire is deleted from the protocol but will be held separately as a standalone document.

Description of Changes:

Global:

Change: Editorial changes (including typographical, grammatical and formatting) have been made throughout the document

Section: Summary Table of Study Protocol

Replace:

EU Post Authorization Study (PAS) Register No	<<Insert Number>>

With:

EU Post Authorization Study (PAS) Register No	**EUPAS31188**

Section 5: Amendments and Updates

Replace:

Amendment or Update No.	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
1	11 April 2019	6	Superseding amendment	Updated timelines
2	**17 July 2019**	**6**	**Superseding amendment**	**Updated timelines**

With:

Amendment or Update No.	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
1	11 April 2019	See summary of changes		
2	17 July 2019	See summary of changes		
3	**14 October 2019**	**See summary of changes**		

Section 9.3: Variables

Replace:

The survey questionnaire (Appendix A) includes the following:

With:

The survey questionnaire includes the following:

Section: Appendix A. List of Standalone Documents

Delete: